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Brief Clinical Report

Sperm Acrosome Defects in a Patient With Aarskog-Scott Syndrome

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We describe a man with Aarskog-Scott syndrome. Infertility and recurrent spontaneous abortions were the primary complaints. The andrological examination demonstrated an unusual scrotal anomaly and a defect of sperm acrosomes. © 1996 Wiley-Liss, Inc.

KEY WORDS: Aarskog-Scott syndrome, genital system, male infertility, sperm acrosome, acrosome defect

INTRODUCTION

The Aarskog-Scott syndrome (MIM 305400) is a genetic disorder that most prominently involves the face and skeletal and genital systems [Aarskog, 1970; Scott, 1971; Porteous and Goudie, 1991; Teebi et al., 1993]. The term "faciogenital dysplasia" is used synonymously. Inheritance is X-linked recessive with some minor manifestations in transmitting females [Sugarman et al., 1973]. The condition may be genetically heterogenous as some reports suggest autosomal dominant or autosomal recessive inheritance [Grier et al., 1981; Guion-Almeida and Richieri-Costa, 1992]. The gene for the X-linked form was recently mapped to Xp11.21 and cloned [Glover et al., 1993; Pasteris et al., 1994].

Genital anomalies such as shawl scrotum and cryptorchidism are important findings in the Aarskog-Scott syndrome [Porteous and Goudie, 1991; Teebi et al., 1993]. It is suspected that subfertility may be more common among affected males than in the general population. Here we report on an adult infertile male with Aarskog-Scott syndrome and a specific structural sperm defect.

CLINICAL REPORT

The 32-year-old propositus and his 26-year-old wife presented with infertility of 4 years. Two pregnancies had occurred, but aborted spontaneously in the first trimester. The gynecological evaluation was normal.

In childhood the propositus had undergone surgery for ptosis of the left eyelid, for penile phimosis, and unilateral inguinal hernia. There was no history of cryptorchidism, and the patient reported normal pubertal development. The family history was noncontributary. Of two healthy brothers, one has four children. Both parents are alive and well. According to his own account, the patient is regarded by his relatives as having a distinctly atypical facial and general physical appearance as compared with other relatives. This could be confirmed from family photographs, but relatives were not available for direct examination.

The patient works as a painter and is of normal intelligence. Craniofacial findings (Fig. 1) include a prominent forehead, marked hypertelorism (interpupillary distance 7.5 cm; >97th centile), downslanting palpebral fissures, mild residual ptosis of the left eyelid, midface hypoplasia, prominent central upper incisors, and poorly modeled ear helices. There was mild clinodactyly of the second and fifth fingers and minimal interdigital webbing, but no clear brachyphalangism. Apart from mild pectus excavatum, the skeletal system was otherwise unremarkable. The patient is shorter (168 cm) than his brothers (175 and 180 cm, respectively) and parents (both 172 cm). There were no prepenile scrotal folds (shawl scrotum), but the scrotum was located in an unusual anterior position. Before the diagnosis of Aarskog-Scott syndrome was entertained, this scrotal anomaly had been independently noted by the referring urologist. Both testicles were in the scrotum and normal on palpation and ultrasound examination [Behre et al., 1989].

Chromosome analysis on cultured blood lymphocytes showed a normal karyotype in the patient and his wife. The patient's serum levels of luteinizing hormone,

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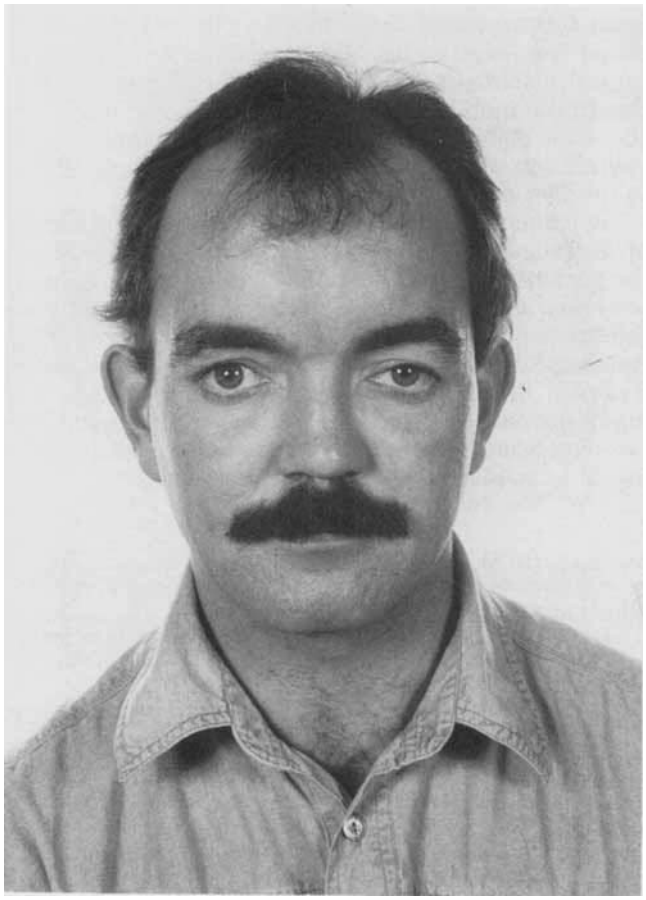

Fig. 1. Patient at age 31 years.

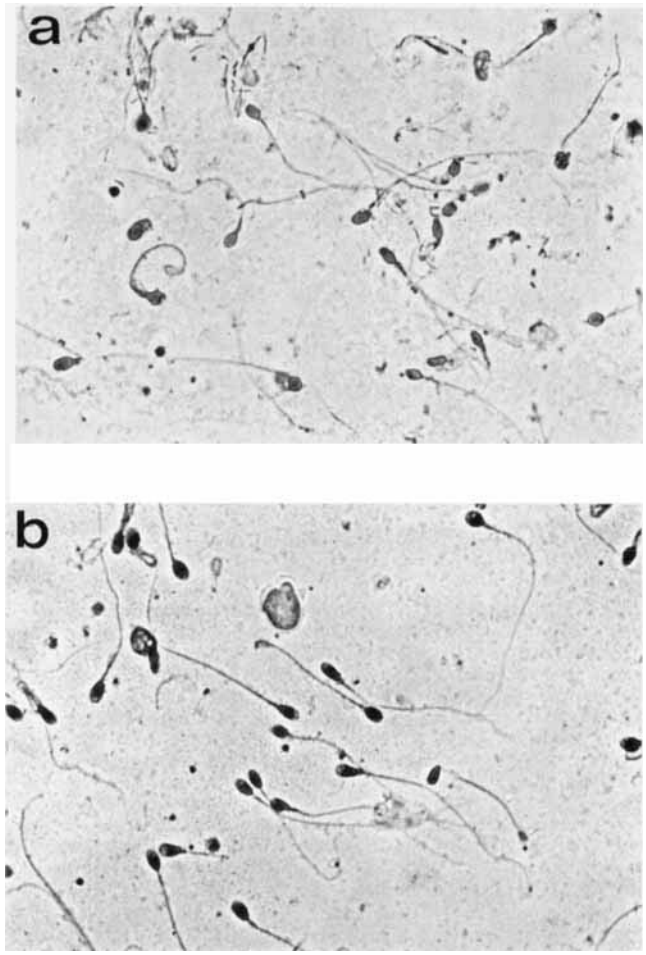

Fig. 2. Sperm from the patient with Aarskog-Scott syndrome (**a**) and a normal fertile control (**b**). Note that almost all sperm in (a) appear to lack an acrosomal cap.

follicle-stimulating hormone, prolactin, testosterone, and estradiol all fell within the normal ranges. Two ejaculate analyses were performed 4 months apart. Total sperm counts were normal. The percentage of progressively motile sperm was 21 in the first and 29 in the second specimen (reference value: ≥50% [WHO, 1992]). Sperm were screened for morphological abnormalities with brightfield light microscopy. Only one of 100 cells analyzed from the first semen sample scored normal (reference value: ≥30% cells with normal morphology). Apparently, 95% of the spermatozoa lacked the acrosome (Fig. 2). On repeat examination, there were 3% sperm scoring normal and 95% lacking the acrosome. Sperm from the second sample were analyzed with transmission electron microscopy [Zamboni, 1987]. Not a single normal cell was detected at this level of resolution. One sperm had a normal appearing head, but the midpiece was disorganized (Fig. 3a). In more than 100 cells analysed, the acrosome was missing altogether, incompletely formed, or dissociated from the nucleus to various degrees (Fig. 3b–d). A subpopulation of germ cells displayed a condensed nucleus, a spermatid-like configuration, and cytoplasm surrounding the nucleus, indicating a maturation defect (Fig. 3b–d).

DISCUSSION

Involvement of the genital system is a hallmark of Aarskog-Scott syndrome. The shawl scrotum anomaly is present in 75–80% of male patients with this disorder [Porteous and Goudie, 1991; Teebi et al., 1993]. The prepenile scrotal folds usually disappear during puberty [Fryns, 1992]. Even in the absence of this characteristic anomaly, the clinical picture in our patient was sufficiently distinct to make the diagnosis of Aarskog-Scott syndrome with confidence. In addition to the abnormality of scrotal position, he had many of the other manifestations of the disease, especially in the craniofacial region.

About two-thirds of males with Aarskog-Scott syndrome have a history of cryptorchidism [Porteous and Goudie, 1991; Teebi et al., 1993]. Puberty is frequently delayed [Fryns, 1992]. It is suspected that males with Aarskog syndrome may be subfertile, possibly as a sequel of cryptorchidism. However, we are not aware of studies addressing this issue systematically. History and laboratory data document a marked impairment of fertility in our patient. The most prominent finding was severe teratozoospermia with defective acrosomes. The acrosome normally caps the sperm head and contains enzymes important for sperm-egg interaction [Schill

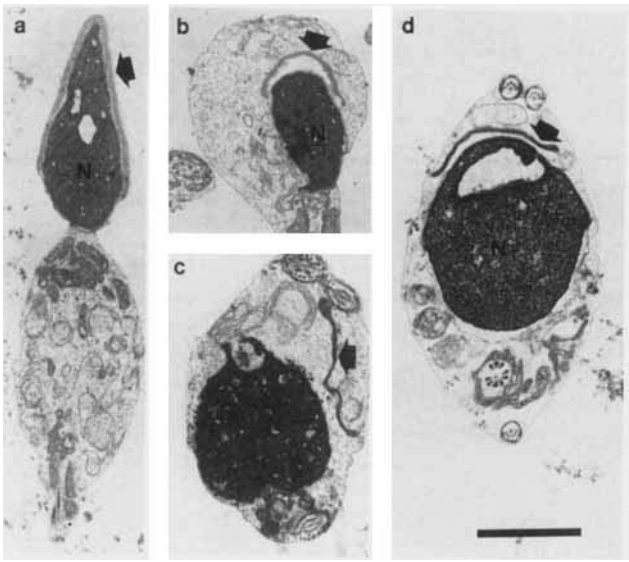

Fig. 3. Ultrastructure of sperm heads from patient with Aarskog-Scott syndrome (magnification × 10,000, bar = 2 μm). Acrosome is indicated by arrows. N = nucleus. (**a**) The only sperm with a normal head structure found among >100 cells examined. Note disorganized midpiece. Mitochondria are not placed in a sheath-like arrangement as usual. Many mitochondria have no discernible internal membranes and an amorphous matrix. (**b**) In this cell the acrosome is too small and dissociated from the nucleus. The sperm head is embedded in abundant cytoplasm. (**c**) Abnormally shaped acrosome that has completely lost contact with the nucleus. The cytoplasm surrounding the nucleus contains axonemal structures and membrane stacks. (**d**) Detached and abnormally small acrosome. Incomplete condensation of the chromatin. Mitochondria, some degenerated, and axonemal structures are visible in the cytoplasm.

et al., 1988]. The organelle is derived from the Golgi apparatus during spermiogenesis [Holstein and Roosen-Runge, 1981]. The biochemical and genetic basis for the transformation of the Golgi apparatus into the acrosome is poorly understood.

In general, teratozoospermia can be of the specific or the unspecific type. The presence of heterogenous defects of sperm heads, midpieces, and tails in one semen sample signifies unspecific teratozoospermia. In cases of specific type teratozoospermia, one uniform morphological abnormality is present in all or most spermatozoa. For example, globozoospermia ("round head defect" of sperm; MIM 102530) is a characteristic, although exceedingly rare specific defect. In its typical form, this abnormality is characterized by rounded shape and vacuolated internal structure of the sperm head and complete absence of acrosomes in all spermatozoa [Zamboni, 1987].

A few of our patient's sperm did carry acrosomes visible at the light microscopic level, but electron microscopy showed them to be structurally abnormal. The rounded shape and nuclear vacuoles typical of globozoospermia were not seen. Our patient's specific sperm defect, therefore, is distinct from globozoospermia, a point substantiated by the fact that the patient had induced two pregnancies. This would not be expected in typical globozoospermia, where infertility is absolute due to the inability of sperm to bind to and penetrate the zona pellucida [Schill, 1991]. It remains open to speculation whether the two miscarriages were related to the sperm defect.

We cannot exclude that the concomitant occurrence of Aarskog-Scott syndrome and an acrosomal defect in our patient is coincidental. However, a pure chance association is improbable considering the rarity of both conditions. We suggest that other adult males with Aarskog-Scott syndrome be screened for sperm abnormalities. Should our observation be confirmed, this might not only shed light on an important aspect of the Aarskog-Scott syndrome, but also allow new insights into the complex process of spermiogenesis.

REFERENCES

Aarskog D (1970): A familial syndrome of short stature associated with facial dysplasia and genital anomalies. J Pediatr 77:856–860.

Behre HM, Nashan D, Nieschlag E (1989): Objective measurement of testicular volume by ultrasonography: Evaluation of the technique and comparison with orchidometer estimates. Int J Androl 12: 395–403.

Fryns JP (1992): Aarskog syndrome: The changing phenotpye with age. Am J Med Genet 43:420–427.

Glover TW, Verga V, Rafael J, Barcroft C, Gorski JL, Bawle EV, Higgins JV (1993): Translocation breakpoint in Aarskog syndrome maps to Xp11.21 between ALAS2 and DXS323. Hum Molec Genet 2:1717–1718.

Grier RE, Farrington EH, Kending R, Manunes P (1981): Autosomal dominant inheritance of the Aarskog syndrome. Am J Hum Genet 33:64A.

Guion-Almeida ML, Richieri-Costa A (1992): Aarskog syndrome in a Brazilian boy born to consanguineous parents. Am J Med Genet 43:808–810.

Holstein AF, Roosen-Runge EC (1981): "Atlas of Human Spermatogenesis." Berlin: Grosse Verlag.

Pasteris NG, Cadle A, Logie LJ, Porteous MEM, Schwartz CE, Stevenson RE, Glover TW, Wilroy RS, Gorski JL (1994): Isolation and characterization of the faciogenital dysplasia (Aarskog-Scott syndrome) gene: A putative rho/rac guanine nucleotide exchange factor. Cell 79:669–678.

Porteous MEM, Goudie DR (1991): Aarskog syndrome. J Med Genet 28:44–47.

Schill W-B, Töpfer-Petersen E, Heissler E (1988): The sperm acrosome: functional and clinical aspects. Hum Reprod 3:139–145.

Schill W-B (1991): Some disturbances of acrosomal development and function in human spermatozoa. Hum Reprod 6:969–978.

Scott CI (1971): Unusual facies, joint hypermobility, genital anomaly and short stature: a new dysmorphic syndrome. Birth Defects OAS VII(6):240–246.

Sugarman GI, Rimoin DL, Lachman RS (1973): The facial-digital-genital (Aarskog) syndrome. Am J Dis Child 126:248–252.

Teebi AS, Rucquio JK, Meyn MS (1993): Aarskog syndrome: Report of a family with review and discussion of nosology. Am J Med Genet 46:501–509.

World Health Organization (1992): "WHO Laboratory Manual for the Examination of Human Semen and Sperm-Cervical Mucus Interaction," 3rd ed. Cambridge: Cambridge University Press.

Zamboni L (1987): The ultrastructural pathology of the spermatozoon as a cause of infertility: The role of electron microscopy in the evaluation of semen quality. Fertil Steril 48:711–734.